UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' BRIEF IN OPPOSITION TO DEFENDANTS' *DAUBERT* MOTION TO PRECLUDE GENERAL CAUSATION OPINIONS OF PLAINTIFFS' EXPERT DIPAK PANIGRAHY, M.D.

MARTIN, HARDING & MAZZOTTI, LLP
1 Wall Street
PO Box 15141
Albany, New York 12212-5141
Tel.: 518-862-1200
Fax: 518-389-6679
rosemarie.bogdan@1800law1010.com

On the Brief:
Rosemarie Riddell Bogdan, Esq.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

ARGUMENT

POINT I: DR. PANIGRAHY'S METHODOLOGY WAS EXHAUSTIVE, RELIABLE AND MEETS AND EXCEEDS ALL DAUBERT REQUIREMENTS FOR RELIABILITY.

A. Dr. Panigrahy's Methodology to Support his Carcinogenicity Causation Determination is Accepted and Reliable.

Plaintiffs' expert, Dr. Dipak Panigrahy, is a pre-eminent cancer researcher who has been researching cancer causation and mechanisms of cancer initiation and promotion for 30 years. He earned his medical degree in 1994 from Boston University; was a surgical resident from 1994-1996; a Research Fellow in Vascular Biology, Department of Surgery under Dr. Judah Folkman at Boston Children's Hospital; was an instructor in surgery (2003-2013) and pathology (2013-2014) at Harvard Medical School; is an Assistant Professor of Pathology at Harvard Medical School since 2014 and has worked in cancer research and the study of carcinogenesis since 1994. Currently, he leads his cancer research laboratory at the Center for Vascular Biology Research, Beth Israel Deaconess Medical Center in Boston, Massachusetts. Following graduation from medical school in 1994 as an M.D., he went into cancer research and helped to establish advanced angiogenesis and cancer animal models which are a foundation for studying mechanisms of cancer causation today; led most of the *in vivo* tumor studies at the Folkman Laboratory at Boston Children's Hospital; has studied many animal tumor models to understand the initiation and promotion of cancer and has expertise in testing anti-cancer drugs and critically evaluating mechanisms of cancer causation. He has his own laboratory for cancer research in which he uses NDMA and NDEA to cause cancer in laboratory animals so he is familiar with these genotoxins. His lab has won over 50 awards for studies on carcinogenesis. Instead of becoming a licensed clinician, Dr. Panigrahy chose to devote his career to cancer research. To suggest he is not qualified

to offer opinions on chemical carcinogenesis, or their genotoxic mechanisms is not credible.[1,2,3] Dr. Panigrahy analyzes epidemiology studies in his professional career as a cancer research scientist and he is offering his opinions from this perspective.[4] A medical doctor does not have to be an epidemiologist to testify regarding epidemiological studies if the expert is qualified by training and experience to interpret such studies. *In re Mirena IUD Products Liability Litigation,* 169 F. Supp 3d 396, 426 (2016), *In re Roundup*, 390 F. Supp. 3d 1102, 1148 (2018).

Dr. Panigrahy's investigation entailed an exhaustive analysis of available scientific research studies and data concerning NDMA and NDEA. His analysis formed his opinions that the NDMA and NDEA in Valsartan Containing Drugs (VCDs) can cause or increase the risk of various cancers in humans based on the **totality** of scientific evidence. His thorough investigation is culminated in a 255-page report, which includes cites to 586 references. Dr. Panigrahy analyzed scientific data that addressed the following which includes the Bradford Hill criteria: plausibility/bio plausibility, strength of association, consistency of association, specificity of association, temporality, dose-response (biologic gradient), coherence, experiment, and analogy.

Dr. Panigrahy explained that he used the same methods he would use if conducting research for scientific publication. He explained that his methodology is consistent with that followed by cancer research scientists investigating if a chemical is a human carcinogen and whether exposure to an agent increases risk of developing cancer.[5]

Dr. Panigrahy reviewed over 1,000 relevant published peer-reviewed scientific studies and medical literature[6], records from this litigation obtained in discovery, and relied on his extensive

[1] Ex. A, Panigrahy Expert Report, pp. 1-5.
[2] Ex. B, Panigrahy CV.
[3] Ex. C, Panigrahy deposition, p. 79.
[4] Ex. C, Panigrahy deposition, p. 567.
[5] Ex. A, Panigrahy Expert Report, pp 15-16.
[6] Ex. C, Panigrahy deposition, p. 28, 36.

scientific knowledge of cancer causation and carcinogenesis. Dr. Panigrahy analyzed scientific data from animal cancer bioassays, mechanistic studies of biological activity in animal tissue and cells, mechanistic studies of biological activity in human tissue and cells, and human epidemiology studies. [7]

Because NDMA and NDEA are recognized by the FDA as Class 1 genotoxic carcinogens,[8,9] there are no randomized control trials (RCTs) in which humans were intentionally exposed to NDMA and NDEA and compared to a control group. This type of human trial has not occurred and is unethical to perform as confirmed by Defendants' experts.[10,11] Since NDMA and NDEA are well studied carcinogens, there is a substantial wealth of other scientific data from both animals and human tissue and cell studies as well as epidemiological studies regarding incidental exposure to NDMA/NDMA that can be analyzed for general causation purposes.

Dr. Panigrahy considered *in vivo* studies such as short and long-term chemical carcinogenesis bioassays in experimental animals, which is the most globally accepted method of identifying human carcinogens. Dr. Panigrahy's research revealed that no species is resistant to the carcinogenic effects of NDMA and NDEA.[12] There is no commercial use of NDMA or NDEA except in research laboratories to *cause cancer* in research animals. Dr. Panigrahy's laboratory uses NDMA and NDEA for this exact purpose, unlike any of Defendants' experts.

In the absence of human scientific testing of a carcinogen, chemical agents for which there is sufficient evidence of carcinogenicity in experimental animals are "presumed human

[7] Ex. A, Panigrahy Expert Report, p. 17.
[8] Ex. D, Control of Nitrosamine Impurities in Human Drugs: Guidance for Industry; FDA Center for Drug Evaluation and Research (CDER), February 2021; p. 5, Appendix B.
[9] Ex. E, ICH M7(R1) Assessment & Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk; Guidance to Industry, March 2018, p. 10.
[10] Ex. F, Deposition excerpt of defense expert Dr. George Johnson, pp. 264-265.
[11] Ex. G, Deposition excerpt of defense expert Dr. Lewis Chodosh, pp. 60-61.
[12] Ex. A, Panigrahy Expert Report, p. 32.

carcinogens."[13] In his report, Dr. Panigrahy identified over 120 peer-reviewed publications by over 100 different laboratories worldwide over the past 60 years which demonstrated that NDMA and NDEA caused cancer in a wide variety of animal models with over 10 tumor types.[14]

Dr. Panigrahy considered the mechanistic studies on animal and human tissue and cells exposed to NDMA and NDEA. He reviewed and analyzed hundreds of *in vitro* studies by different laboratories worldwide over the past 60 years which demonstrated that NDMA and NDEA caused adduct formation in a wide variety of animal and human tissue with over 10 tumor types as detailed in his expert report. His Bradford Hill analysis for both NDMA and NDEA identify these studies which he references for each cancer type.

Dr. Panigrahy analyzed available human epidemiological studies (dietary and occupational) which quantified exposures to NDMA and NDEA. He discussed each study that quantified exposure with a statistically significant increased risk and those that did not. Dr. Panigrahy evaluated the cumulative exposures to NDMA or NDEA in the dietary and occupational studies that resulted in a statistically significant increased risk of certain cancers, and compared them to the amounts of NDMA and NDEA in VCDs to explain how the doses of NDMA and NDEA in VCDs can cause human cancer. He also evaluated the two VCDs studies, one authored by Pottegard and the other by Gomm, described the limitations of each study and weighted them accordingly.[15]

Dr. Panigrahy reviewed the worldwide scientific and regulatory agencies findings for NDMA and NDEA including the World Health Organization (WHO)/ International Agency for Research on Cancer (IARC); United States National Toxicology Program (NTP); United States

[13] Ex. A, Panigrahy Expert Report, p. 18.
[14] Ex. A, Panigrahy Expert Report, pp. 19-20.
[15] Ex. A, Panigrahy Expert Report, pp.95-96

Environmental Protection Agency (EPA); US Department of Health and Human Services (DHHS); Environment Canada and Health Canada; the European Medicines Agency (EMA); Australian Government Department of Health; Therapeutic Goods Administration (TGA) and Pharmaceuticals and Medical Devices Agency (PMDA-Japan).

Dr. Panigrahy identified how animal data on carcinogenicity has preceded and predicted later epidemiological observations in humans and that the cellular and molecular changes leading to cancer in animals, mammals and humans are virtually identical,[16] particularly in the capability of NDMA and NDEA to form O6-methyguanine and N7-methylguanine in DNA of tissues in both animals and humans.[17] Dr. Panigrahy reviewed the many rodent studies as well as large animal and primate models and discussed how these large animals have many fundamental similarities to humans including anatomic, physiological, genomic, proteomic, immunologic, and nutritional similarities.[18]

Dr. Panigrahy testified to all the studies and scientific data that he reviewed and considered in forming his opinions consistent with his report.[19] To reach his opinions, Dr. Panigrahy did not rely on any one study or paper or theory. He considered and analyzed all the above scientific information including studies which were not supportive, and he described his reasons for assigning different weight to the various studies. After analyzing all this scientific data, Dr. Panigrahy performed an analysis using the accepted Bradford Hill criteria of causation when assessing the causal relationship between NDMA and NDEA and human cancer and weighed the evidence accordingly. Both the weight of evidence methodology and Bradford Hill are well-accepted methodologies in the Third Circuit: "we accept that the Bradford-Hill and weight of

[16] Ex. C, Panigrahy deposition, pp. 184-185; 212, 348.
[17] Ex. C, Panigrahy deposition, p. 94.
[18] Ex. A, Panigrahy Expert Report, pp. 23-24.
[19] Ex. C, Panigrahy deposition, pp. 134-135; pp. 293-294.

evidence analyses are generally reliable." *In re Zoloft (Sertraline Hydrochloride) Products Liability Litigation*, 858 F.3d 787, 796-797 (3rd Cir. 2017). After analyzing each type of scientific evidence, Dr. Panigrahy found overwhelming evidence that NDMA and NDEA are carcinogens that can cause several human cancers via multiple biologically plausible mechanisms. Dr. Panigrahy provided his opinions within a reasonable degree of scientific certainty and supported his findings and opinions with a preponderance of the evidence.

B. The Use of the Totality of Scientific Evidence to Support a Carcinogenicity Causation Determination is Well Accepted.

The use of the totality of scientific evidence to support a carcinogenicity causation determination is not only accepted but preferred. In the *Reference Manual on Scientific Evidence; Reference Guide on Epidemiology*, by Michael Green, et.al, Third Edition, 2011 by the Federal Judicial Center, a reference work frequently cited and relied upon by federal courts, there is a citation to *Modern Criteria to Establish Human Cancer Etiology,* by Carbone, 64 Cancer Res. 5518, 5522 (2004) stating "There should be no hierarchy [among different types of scientific methods to determine cancer causation]. *Epidemiology, animal, tissue culture and molecular pathology should be seen as integrating evidence in the determination of human carcinogenicity,*" (emphasis added). This is exactly the methodology followed by Dr. Panigrahy and why his analysis is scientifically based and reliable.

In the Third Circuit, an expert's opinion is admissible, if the process or technique used is reliable, and the methods and procedures are based on science "rather than on the subjective belief or unsupported speculation". *In re Paoli*, 35 F.3d 717, 742 (1994); *In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Practices & Prods. Litig."* 509 F. Supp. 3d 116, 131 (2020).

In the case of *In re Johnson & Johnson Talcum Powder,* 509 F. Supp. 3d 116 (2020), the District of New Jersey was faced with admissibility of expert testimony for general causation.

Plaintiffs offered several experts to show that the use of talc can cause ovarian cancer. *Id* at 456. One of plaintiffs' experts, a medical doctor, considered a wide body of relevant epidemiological evidence, including "statistical data, strengths and weaknesses of study type, effect of bias, chance, confounding and differences in exposure measures. She considered dose response, data from non-epidemiologic lines of evidence such as animal, cell, clinical and pathological studies." *Id* at 525. Ultimately, Plaintiffs' expert found a relative risk factor of 1.2 to 1.6, which the Court held was sufficient for purposes of general causation. Id at 575. The Court stated that "[i]n epidemiology, there is, however, no threshold, or a magical number, of a relative risk that must be found in order to place significant weight on the strength of association factor. Indeed, "[a] relative risk of 2.0 is not so much a password to a finding of causation as one piece of the evidence, among others for the court to consider in determining whether an expert has employed a sound methodology in reaching his or her conclusion." *Id* at 538 (Citing *Magistrini*, 180 F. Supp. 2d at 606 (quoting *Landrigan v. Celotex Corp.*, 127 N.J. 404, 419, 605 A.2d 1079 (1992))."

As in the *Talcum* decision above, the Third Circuit has accepted an expert's consideration of a wide body of evidence which include animal studies, animal and human cell, clinical and pathological studies, epidemiological studies, and Bradford Hill analysis as a reliable methodology to offer a general causation opinion. This is exactly the methodology followed by Dr. Panigrahy in this case.

Like our case, the Court in *In re Roundup Prods. Liab. Litig.,* 390 F. Supp. 3d 1102 *(2018)* considered the admissibility of expert testimony for general causation. Id at 1108. Much like NDMA and NDEA, *In re Roundup* dealt with glyphosate, a cancer initiator and promoter. *The Roundup* Court agreed that biological plausibility was properly supported by mechanistic evidence stating: "…that glyphosate causes damage to the genetic material in cells (genotoxicity) or an

imbalance between the production of reactive oxygen species and antioxidant defenses in a cell (oxidative stress) supports the plaintiffs' argument that it is biologically plausible that glyphosate acts as a carcinogen. 390 F. Supp. 3d at 1129. Like *In re Roundup*, evidence of genotoxic damage to the genetic material in cells with reactive oxygen species and oxidative stress in both humans and animals is part of Dr. Panigrahy's opinions that NDMA and NDEA are human carcinogens.[20]

The Plaintiffs' experts in *Roundup* used the Bradford Hill criteria and surveyed a significant amount of epidemiological evidence, including occupational studies (*Id* at 1118), as well as animal studies (*Id* at 1126), and mechanistic data. *Id* at 1129. **The Court found that "in light of all the available evidence, that a causal interpretation *is appropriate*".** *Id* at 1152 (emphasis added). The Court concluded that plaintiffs' experts "have surveyed the significant body of epidemiological literature relevant to this question; identified at least a few statistically significant elevated odds ratios from case-control studies and meta-analyses; identified what they deem to be a pattern of odds ratios above 1.0 from the case-control studies, *even if not all are statistically significant*; emphasized that studies of glyphosate have focused on many different types of cancer but found a link only between glyphosate and NHL; given legitimate reasons to question the results of the primary study on which Monsanto relies; and concluded, in light of all the available evidence, that a causal interpretation is appropriate." *Id* at 1152 (emphasis added). *Roundup* confirmed that consideration of the Bradford Hill factors (as done by Dr. Panigrahy for each cancer type he identified) "is a reliable method for determining causation as a general matter…". 309 F. Supp. 3d at 1130.

[20] Ex. A, Panigrahy Expert Report, pp. 44-76;153-177.

Dr. Panigrahy used the same type of available scientific evidence to reach his general causation opinion here. This is a well-established appropriate methodology to reach an opinion on general causation. *In re Roundup Prods. Liab. Litig.,* 390 F. Supp. 3d 1102, 1130.

Similarly, the Court in *In re Actos Pros. Liab. Litig.,* 2013 U.S. Dist. LEXIS 179235 (2013) considered the admissibility of expert testimony for general causation. The drug in *Actos* was pioglitazone, which, as here, has also been classified by IARC as a class 2A carcinogen. Plaintiffs' experts opined that one year of exposure was sufficient for the development of bladder cancer and supported this theory with animal studies and with two clinical trials. *Id.* at 36-37. The Court held that the experts sufficiently applied the *Daubert* factors to each piece of evidence presented and met the threshold showing for general causation. *Id* at 67-69. Notably, Dr. Panigrahy served as an expert in the Actos litigation, and his opinions were accepted by the Court.

POINT II: DR. PANIGRAHY DOES NOT USE A "SINGLE MOLECULE THEORY" IN HIS ANALYSIS OR TO FORM HIS OPINIONS, WHICH ARE BASED ON RELIABLE METHODS AND SCIENTIFIC DATA.

The Defendants' *Daubert* motion to preclude Dr. Panigrahy repeatedly misrepresents, mis-states and misconstrues Dr. Panigrahy's testimony, report, methodology and opinions. Defendants misrepresent that Dr. Panigrahy relies on a "single molecule theory" for his opinions that NDMA and NDEA can cause human cancer. This is simply inaccurate.

He explains that NDMA and NDEA undergo metabolic activation to induce cancer. In his report and during his deposition he showed that the cancer-causing activity of NDMA and NDEA result from their metabolic transformation within susceptible tissues in the body to chemically reactive agents which either methylates (NDMA) or ethylates (NDEA) DNA forming DNA adducts.[21] When acting as an initiator, NDMA and NDEA can cause cancer when the initial

[21] Ex. A, Panigrahy Expert Report, pp. 46-47; 155-156; Ex. C, Panigrahy deposition, pp. 94-95.

ingested NDMA and NDEA molecule must undergo bioactivation to an electron-seeking molecule (called an electrophile) that binds to DNA to form addition products, known as adducts, which lead to DNA damage and mutations. DNA adducts are segments of DNA bound to a cancer-causing chemical. The formation of DNA adducts is a key process that initiates the transition to a cancerous cell from a normal cell (carcinogenesis). Dr. Panigrahy explains that it is the ability of carcinogens to form DNA adducts that initiate and can lead to cancer.[22]

It is this molecular DNA damage that Dr. Panigrahy is referring to when he explains that one molecule of NDMA or NDEA can initiate the process which causes cancer, but then goes on to explain it is not likely and could take several molecules.[23]

When referencing "one molecule" in his report, Dr. Panigrahy is explaining the biomechanism in which NDMA and NDEA initiate cancer that happens as a result of molecule-to-molecule interaction. He explains this is why there is no safe exposure threshold for genotoxic chemicals like NDMA and NDEA, and that one molecule of NDMA or NDEA can disrupt the DNA and lead to mutation that can lead to cancer.[24] This opinion is based on the well accepted principle of the mechanism of action of genotoxins.

Peto (1991) is the seminal animal study used by the FDA and other worldwide agencies to show both NDMA and NDEA have classic dose response including at low doses to cause cancerous tumors. The Peto study found that a linear relationship was observed at low doses (below 1 ppm) suggesting that a dose of 1 ppm of NDMA in drinking water would cause about

[22] Ex. A, Panigrahy Expert Report, pp. 46-47.
[23] Ex. C, Panigrahy deposition, pp. 603, 609 wherein Dr. Panigrahy explains that what scientists have shown is that one molecule of a genotoxic, mutagenic, clastogenic chemical can induce a mutation to cause cancer, and explains when he says "can," he doesn't say one molecule "will" likely cause cancer. but he cites plenty of papers that support a mutagenic substance such as NDMA/NDEA-- can lead to a cancer.
[24] Ex. C, Panigrahy deposition, p. 603; Ex. A, Panigrahy Expert Report, p. 83.

25% of the animals to develop a neoplasm. Peto also found no indication of a threshold. The summary of the Peto study states: "The linear relationship observed at low dose rates (below 1 ppm) suggests that under these *experimental conditions, among rats allowed to live their natural life span, a dose of 1 ppm of NDEA or NDMA in the drinking water will cause about 25% to* develop a liver neoplasm, a dose of 0.1 ppm will cause about 2.5% to do so, and a dose of 0.01 ppm will cause about 0.25% to do so etc., with no indication of any 'threshold.'" Dr. Panigrahy addresses the "no safe level" and "no observed effect level" concepts as they apply to genotoxins generally to explain the linear dose extrapolation used by the FDA.[25]

However, for Defendants to argue that Dr. Panigrahy's theory of causation is based on the "one molecule" or "no safe level" theory is disingenuous in light of his determination of the **lifetime cumulative dose exposures** to NDMA and NDEA associated with a statistically significant increased risk of cancers as shown in human epidemiology studies. He analyzed the epidemiological studies that quantified the amount of NDMA and/or NDEA to which the cohorts were exposed. This data allowed for a calculation of the total NDMA or NDEA exposure associated with increased risk of cancer as discussed in Point III below. Similarly, the Defendants' bald assertion that Dr. Panigrahy ignored the background rate is equally unfounded. As in all the epidemiology studies considered, the background rate of NDMA would be exemplified by the NDMA or NDEA exposures experienced by the individuals in the first quartile (tertile or quintile) of exposure that did not have an increased risk of cancer.[26] Lifetime cumulative exposure has been admitted in other Courts; *Berman v. Mobil Shipping & Transp., Co.,* 2019 WL 1510941*; Gorton v. Air & Liquid Sys. Corp.,* 2020 WL 4193649 (Mid. Dist, Pennsylvania) *and Hoffeditz v.*

[25] Ex. A, Panigrahy Expert Report, pp. 83-85.
[26] Ex. C, Panigrahy deposition, pp. 487, 619.

AM Gen, LLC, 2017 WL 3332263 (D.N.J., 2017) *relied upon by Defendants which actually permitted a lifetime cumulative analysis.*

The cases cited by Defendants in their motion are inapplicable to the facts of this case or are easily distinguished. *Hardeman v. Monsanto, Co.,* 997 F. 3d 941 (9th Cir., 2021) supports Dr. Panigrahy's analysis as it affirms reliance upon multiple pieces of evidence, epidemiology, animal, and cellular studies for general causation purposes. *Soldo v. Sandoz Pharms. Corp*., 244 F. Supp. 2d 434 (3d Cir., 2003) is also distinguished as there was a lack of any statistically significant epidemiological studies that related drug compounds to an increased risk of stroke; *McMunn v. Babcock & Wilcox Power Generation Group, Inc*., 2013 US Dist. LEXIS 100259; 2013 WL 3487560 (2013) was a specific causation case involving atmospheric radiation exposure where the expert did not examine dose exposure. *Amorgianos v. Amtrak*, 303 F. 3d 256 (2002) was a specific causation case stating that an expert opinion based on unsupported data, methods or studies was not admissible.

POINT III: DR. PANIGRAHY PROVIDED A SCIENTIFICALLY DERIVED METHOD USING EXISTING HUMAN EPIDEMIOLOGY STUDIES TO ASCERTAIN THE TOTAL CUMULATIVE EXPOSURE LEVELS WHICH RESULT IN A STATISTICALLY SIGNIFICANTLY INCREASED RISK OF SPECIFICALLY IDENTIFIED CANCERS.

Contrary to Defendants' contention, Dr. Panigrahy does not use the single molecule theory or the FDA's acceptable intake level of 96 nanograms per day as a proxy for general causation. To the contrary, Dr. Panigrahy supports his general causation opinion regarding dose with peer reviewed human epidemiology studies that quantified NDMA exposure, found dose-response, and **statistically significant increased risks** of specific cancers. This is absolutely an accepted methodology for demonstrating the exposures that can cause cancer.

Contrary to the Defendants' assertion, relative risks of 2.0 or higher are not required. There is no such requirement in the Third Circuit. *Talcum,* 509 F. Supp.. 3d 116 at 162-164. (relative risk of 1.2 to 1.6 deemed acceptable to Court which noted there is no bright line rule as long as the relative risk is above 1.0). *Id* at 164, fn 37. In *Talcum*, the Court explained there was no threshold or magical number of relative risk that must be found.: Citing *Magistrini*, 180 F. Supp. 2d at 606 (quoting *Landrigan v. Celotex Corp.*, 127 N.J. 404, 419, 605 A.2d 1079 (1992)). *In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Practices & Prods. Litig.,* 509 F. Supp. 3d 116 at 163-164.

"I note that in the context of relative risk, courts have endorsed "a flexible *Daubert* inquiry rather than bright-line rules." *Pritchard*, 705 F. Supp. 2d at 486 (concluding that "a relative risk of 2.0 is not dispositive of the reliability of an expert's opinion relying on an epidemiology study, but it is a factor, among others, which the Court is to consider in its evaluation"). **Accordingly, in the context of relative risk on a *Daubert* motion, the Court's role is to determine whether the expert has reliably arrived at, based on sound scientific methods, a relative risk that in his or her view could be clinically significant.** *See, e.g.*, *Pick v. Am. Med. Sys., Inc.*, 958 F. Supp. 1151, 1160 (E.D. La. 1997) ("A relative risk above 1.0 is statistically significant, even if not sufficient, by itself, to establish causation by a preponderance of the evidence."); *Miller v. Pfizer Inc.*, 196 F. Supp. 2d 1062, 1079 (D. Kan. 2002) (declining to find, as a matter of law, that a relative risk must be above a certain number to be clinically significant)". *In re Johnson & Johnson Talcum Powder Prods. Mktg., Sales Practices & Prods. Litig.,* 509 F. Supp. 3d 116 at 164, fn 37.

As detailed below, there are many studies cited by Dr. Panigrahy that find a statistically increased risk of specific cancers some of which have ORs, RRs or HRs of more than 1.0 but less

than 2.0, and many others which have values of 2.0 or higher.[27] These studies are one piece of the evidence to support Dr. Panigrahy's general causation opinion.

Dr. Panigrahy's literature search identified human dietary studies which quantified daily dietary exposure to NDMA and/or NDEA and measured the risk of various cancers. He calculated the cumulative doses associated with the following dietary studies that found a statistically significant increased risk of a particular cancer: DeStefani gastric cancer study (OR 3.6, 95% CI 2.4-5.5); Pobel gastric cancer study (OR 7.00; 95% CI: 1.85 to 26.46); LaVecchia gastric cancer study (OR 1.4; 95% CI 1.1-1.7); Larsson gastric cancer study; HR 1.96; 95% CI 1.08-3.58 ; Loh colorectal cancer study (HR: 1.46; 95% CI: 1.16, 1.84); DeStefani lung cancer study (OR 3.14, CI: 95%, 1.86-5.29) and Goodman lung cancer study (Men OR Q4 v. Q1=3.3, CI: 95%, 1.7-6.2)(Women OR Q4 v Q1=2.7, CI: 95%, 1.0-6.9).[28] The Zheng study allowed him to calculate the associated cumulative dose of NDEA associated with an increased risk of pancreatic cancer. By calculation of these cumulative doses, he demonstrated the cumulative doses of NDMA and NDEA that resulted in a statistically significant increased risk of cancer which is far from relying on a "one molecule" theory.

These studies reported NDMA daily doses for the tertiles/quartiles/quintiles. The studies finding statistically significant increased risks of cancer were the DeStefani gastric cancer study reporting intake of 270 nanograms of NDMA per day; Pobel gastric cancer study reporting

[27] It would be a mistake to place such great weight on the concept of statistical significance. As the ASA has taken great care to note in its 2016 statement on p-values: "Practices that reduce data analysis or scientific inference to mechanical "bright-line" rules (such as "$p < 0.05$") for justifying scientific claims or conclusions can lead to erroneous beliefs and poor decision making. A conclusion does not immediately become "true" on one side of the divide and "false" on the other. *See* Wasserstein et al. The ASA Statement on *p*-Values: Context, Process, and Purpose, The American Statistician (2016),70:2, p. 129-133. Ex. U

[28] Ex. A, Panigrahy Expert Report, pp. 89-90.

intake of 290 nanograms of NDMA per day (75% percentile distribution); Zheng pancreatic cancer study reporting intake of 180 nanograms of NDEA per day; LaVecchia gastric cancer study reporting intake of 190 nanograms of NDMA per day; Larrson gastric cancer study reporting intake of 190 nanograms per day; Knekt colorectal cancer study reporting intake of 53 nanograms of NDMA per day (mean); Loh cancer study reporting intake of 126 nanograms of NDMA per day (Quartile 4); DeStefani lung cancer study reporting intake of 270 nanograms of NDMA per day; and Goodman lung cancer study reporting intake of 700 nanograms per week/100 nanograms per day (Upper bound of Quartile III intake).[29]

Based on these intakes, Dr. Panigrahy summarized the lifetime cumulative exposures of NDMA in the dietary studies based on the reported high exposure category assuming a conservative 60 years of daily intake as follows:[30] DeStefani Gastric Cancer Study = 5,913 micrograms; LaVecchia Gastric Cancer Study = 4,161 micrograms; Knekt Colorectal Cancer Study = 1,160 micrograms (mean); Larsson Gastric Cancer Study = 4,161 micrograms; Loh Colorectal Cancer Study = 2,759 micrograms; DeStefani Lung Cancer Study = 5,913 micrograms; and Goodman Lung Cancer Study = 2,190 micrograms. There is only one NDEA dietary study in Panigrahy's report, Zheng, that quantified the level of NDEA exposure, and that study evaluated the association between NDEA exposure and pancreatic cancer. The daily intake in the Zheng study for the lower bound of the highest quartile was 180 nanograms per day which would equate to a cumulative dose of 3,942 micrograms assuming 60 years of daily intake. Notably, this study found an 89% statistically significant increased risk of pancreatic cancer associated with the daily intake of 180 nanograms.[31]

[29] Ex. A, Panigrahy Expert Report, pp. 88-89; Addendum, p. 1.
[30] Ex. A, Panigrahy Expert Report, pp. 89-91.
[31] Ex. A, Panigrahy Expert Report, p. 195.

Dr. Panigrahy's general causation opinion is also supported by the Hidajat rubber industry occupational study which quantified levels of NDMA exposure and evaluated the risk of cancer mortality related to cumulative NDMA exposure.[32,33] The Hidajat study involved a large cohort of 36,441 males with a long 49-year follow-up period. This study reported a classic dose response relationship between increased exposure to NDMA and increased risk of death from various cancers. Importantly, this occupational exposure study was highlighted by Dr. Panigrahy because the amount of NDMA to which the workers were exposed was quantified. This study was conservative, because of its design as a mortality study, it underestimates the number of cancers.[34] This occurs in mortality studies because a study participant who develops cancer is not counted unless it is the cause of their death on their death certificate. So, for example, a rubber worker who had liver cancer but recovered and then died of an unrelated cause would not be counted in the liver cancer case count.[35]

Notably, there was a statistically significant increased risk of mortality associated with bladder, lung, stomach, multiple myeloma, esophageal, prostate, and pancreatic cancer for cumulative NDMA exposures at the lower bound of Quartile 2, and statistically increased risk of mortality associated with liver cancer, leukemia, and non-Hodgkin's lymphoma at the lower bound of Quartile 3.

The statistically significant risks of increased mortality from certain cancers observed in the Hidajat study were as follows:

---

[32] Ex. H, Hidajat, et. al. *Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow up.* Occupational and Environmental Medicine *(2019)* p. 1.
[33] Ex. A, Panigrahy Expert Report, pp. 86-87.
[34] Ex. H, Hidajat, et. al. *Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow up.* Occupational and Environmental Medicine *(2019)* Table at pp. 253-256.
[35] Ex. A, Panigrahy Expert Report, pp. 96-97.

(1) death from gastric cancer was found to be statistically significant in the second, third, and fourth quartiles (Sub distribution hazard ratio/SHR 1.32, 95% CI:1.10-1.57, SHR 1.62, 95% CI:1.32-1.98, and SHR 1.72, 95% CI: 1.41-2.10 respectively) compared with men in the first quartile (lowest NDMA exposure). A dose-response effect is strongly supported as the P-value for trend of 0.01.

(2) death from lung cancer was statistically significant in the second, third and fourth quartiles (SHR 1.21, 95% CI:1.10-1.32; SHR 1.54 95% CI: 1.39-1.70; and SHR 1.7, 95% CI: 1.54-1.87, respectively) with a P-value for trend of 0.36.

(3) death from prostate cancer was statistically significant in the second (SHR 2.32, 95% CI: 1.82, 2.97), third (SHR 4.87, 95% CI: 3.89, 6.11), and fourth quartiles (SHR 5.36, 95% CI: 4.27, 6.73) with a P-value for trend of less than 0.01.

(4) death from liver cancer was statistically significant in Quartiles 3 and 4 (SHR 1.96, 95% CI:1.16 to 3.29) and (SHR 2.86, 95% CI: 1.78 to 4.59, respectively) with a P-value for trend of 0.03.

(5) death from bladder cancer was statistically significant for the second, third, and fourth quartiles (SHR 1.57, 95% CI: 1.19-2.07; SHR 2.45, 95% CI: 1.87-3.21; and SHR 2.82, 95% CI: 2.16-3.67, respectively) with a P-value for trend of less than 0.01.

(6) death from multiple myeloma was statistically significant in the second, third, and fourth quartiles (SHR 1.59, 95% CI: 1.22-2.08), (SHR 2.78, 95% CI: 2.15-3.60) and (SHR 2.81, 95% CI: 2.17-3.64 respectively) (P-value less than 0.01) with a P-value for trend of less than 0.01.

(7) death from non-Hodgkin's lymphoma and leukemia were statistically significant in the third and fourth quartiles: non-Hodgkin's lymphoma (SHR 2.17, 95% CI: 1.35-3.47 and 2.25, 95% CI: 1.41-3.59, respectively) (P-value 0.11) and leukemia (SHR 3.27, 95% CI: 2.20-4.86 and

3.47, 95% CI: 2.35 to 5.13, respectively) (P-value less than 0.01). This dose-response effect is strongly supported as the P-value for trend was less than 0.01.

(8) death from esophageal cancer was statistically significant in the second, third, and fourth quartiles (SHR 1.7, 95% CI: 1.24-2.33, SHR 2.43, 95% CI:1.78-3.31, and SHR 3.04, 95% CI:2.26-4.09, respectively) compared with men in the first quartile (lowest NDMA exposure) with a P-value for trend of 0.26.

As detailed in Dr. Panigrahy's expert report, his calculations based on the Hidajat data found a cumulative NDMA uptake of 7,488 micrograms in the lower bound of Quartile II, 14,304 mg for the lower bound of Quartile III, and 23,208 micrograms for the lower bound of Quartile IV.[36] As this was an inhalation study, Dr. Panigrahy adjusted the human absorption percentage to 80%, using an accepted method,[37] to account for the amount of the NDMA expected to be exhaled.[38] He arrived at cumulative exposure values as follows: cumulative NDMA exposure of 5,990 micrograms for lower bound of Quartile II (statistically significant increased mortality associated with bladder, lung, stomach, multiple myeloma, esophageal, prostate, and pancreatic cancer); cumulative NDMA exposure of 11,443 micrograms for lower bound of Quartile III (statistically significant increased mortality associated with liver cancer, leukemia and non-Hodgkin's lymphoma) and cumulative exposure of NDMA of 18,566 micrograms for the lower bound of Quartile IV.[39]

In his report, Dr. Panigrahy explains that these studies are examples of cumulative exposures that result in a statistically significant increased risk of cancer but should not be

[36] Ex. A, Panigrahy Expert Report, p.87.
[37] Ex. A, Panigrahy Expert Report, pp. 87-88
[38] Ex. I, The [redacted] by defense expert Fryzek. See Fryzek report pp. 51, 54)
[39] Ex. A, Panigrahy Expert Report, p. 88.

considered as bright line thresholds, and that some of the studies showed statistically significant increased risks at lower tertiles/quartiles/quintiles.[40] By this analysis, Dr. Panigrahy provides evidence of the total cumulative exposures to exogenous NDMA that result in an increased risk of cancer.

Notably, by way of illustration, with the high dose reported by the FDA [redacted][41], a Plaintiff taking [redacted] could reach 1,000 micrograms of exposure in 50 days, 2,000 micrograms of exposure in 100 days, 3,000 micrograms of exposure in 150 days, 4,000 micrograms of exposure in 200 days etc. It should also be noted that Plaintiffs exposed to NDMA and/or NDEA in their VCDs would have this exposure in addition to other exogenous sources of NDMA from diet estimated in the US to range from 0.03 to 0.06 ug/day, depending on age, or 0.08 ug/day when beer is included.[42]

For *In re Roundup*, the plaintiffs' experts relied upon existing human epidemiology studies for dose response showing that humans exposed to glyphosate cumulatively according to usage (*i.e.*, used between zero and two days per year or used more than two to ten days per year) showed statistically significant associations for glyphosate and NHL. *Roundup*, 390 F. Supp. 3d 1102, 1119-1120. Animal toxicology and cancer bioassay studies were also used to determine statistically significant increases in tumor development in a specific dose group of rodents compared to the control. *Id* at 1128. Mechanistic cell studies showing genotoxicity and oxidative stress were also used by the Plaintiffs. The Court stated that these studies supported plaintiffs' argument of biological plausibility and that mechanistic evidence can "greatly strengthen a causal inference." *Id* at 1129.

[40] Ex. A, Panigrahy Expert Report, pp. 89-91.
[41] Ex. A, Panigrahy Expert Report, p. 9.
[42] Ex. A, Panigrahy Expert Report, pp. 88-89.

In this case, Dr. Panigrahy's methodology also used a cumulative dose exposure over time based on observational studies, supported by mechanistic cellular studies, animal toxicology studies, and *in vitro* studies.

POINT IV: DEFENDANTS CONFLATE GENERAL CAUSATION AND SPECIFIC CAUSATION IN THEIR MOTION TO PRECLUDE.

In their motion to preclude, Defendants allege that Dr. Panigrahy was required to "demonstrate the levels of exposure that are hazardous to human beings generally as well as the plaintiff's actual level of exposure." This is simply incorrect. Exposure/dose for an individual plaintiff is not a general causation issue. It is a specific causation issue.[43] As set forth in note 161 of the *Reference Manual on Scientific Evidence*, "evidence of a dose–response relationship as bearing on whether an inference of general causation is justified is analytically distinct from determining whether evidence of the dose to which a plaintiff was exposed is required in order to establish specific causation." [44] Simply put, "General causation is whether a substance can cause an increased risk of a particular injury or condition in the general population. In contrast, specific causation is whether a substance caused a particular individual's injury." (citing *McClain v. Metabolife Int'l. Inc*., 401 F. 3d 1233, 1239 (11th Cir., 2005).

Plaintiffs have clearly demonstrated that the NDMA and NDEA at the levels found in the contaminated VCDs can cause an increased risk of certain cancers by use of peer reviewed published human dietary and occupational studies which showed at certain cumulative NDMA or NDEA exposures persons are at a statistically significant increased risk of cancer. At this general causation stage, the requirements of Daubert are satisfied by Dr. Panigrahy' s use of reliable scientific analysis and data to show that the NDMA and NDEA levels in VCDs "can" reach the

[43] *Reference Manual on Scientific Evidence*, p. 603, note 161.
[44] *Reference Manual on Scientific Evidence*, p. 603, note 161.

levels of exposure shown to cause a statistically significant increased risk of cancer in the human dietary studies and death from cancer in the Hidajat occupational study.

Defendants reframe the general causation question as "Here, the general causation question is whether NDMA or NDEA can cause the cancers alleged by plaintiffs at exposure levels people may have plausibly experienced. *In re Roundup Prod. Liab. Litig*., 390 F. Supp. 3d 1102, 1111 (N.D. Cal., 2018)." Without conceding that this is the proper description of the general causation question in this case or not, it is submitted that Dr. Panigrahy's cumulative dose exposure analysis based on the available human dietary and occupational studies along with his illustration that these levels can be easily reached by the patient population that took contaminated VCDs, more than satisfies this general causation question. Note, each Plaintiff's increased risk will be addressed at the specific causation stage and will be based on their individual cumulative exogenous exposures to NDMA/NDEA. Individual exposure profiles are not required at the general causation stage.

POINT V: DR. PANIGRAHY USES RELIABLE DATA TO SUPPORT HIS OPINIONS AND DOES NOT "CHERRY PICK" AS HE USES THE HIGHER LEVELS OF EXPOSURE TO ILLUSTRATE THE DOSES OF NDMA AND/OR NDEA PATIENTS COULD EXPERIENCE EASILY REACH THE CUMULATIVE EXPOSURE DOSES FOR THE STATISTICALLY SIGNIFICANT QUARTILES IN THE DIETARY AND OCCUPATIONAL STUDIES

For the general causation phase the question is not whether NDMA or NDEA gave cancer to any of the particular Plaintiffs who brought lawsuits, and the Plaintiffs need not establish any particular level of exposure. It is enough in this litigation at the general causation stage for the Plaintiffs to show that NDMA and NDEA can cause the various human cancers when people are exposed to the doses people might plausibly experience. *See In re Roundup Prod. Liab. Litig*., 390 F. Supp. 3d 1102, 1111 (N.D. Cal., 2018).[45]

[45] Employing the results of group-based studies of risk to make a causal determination for an individual plaintiff is beyond the limits of epidemiology. *Reference Manual on Scientific*

Following this reasoning, Dr. Panigrahy gave examples of how a Plaintiff taking 320 mg valsartan with the average level of contamination [redacted] cumulative NDMA exposure for the Hidajat lower bound of Quartile II (5,990 micrograms of NDMA) in 300 days (10 months).[46] Likewise, if the highest reported contamination [redacted] was used as an example, patients could reach the cumulative NDMA exposure levels for Hidajat Quartile II in approximately 100 days. The dietary studies in Dr. Panigrahy's report have lower cumulative levels of NDMA exposure associated with a statistically significant increased risk of cancer so a patient would be able to reach cumulative levels of exposure that would increase the risk of cancer in an even shorter time period. It was appropriate for Dr. Panigrahy to use the average reported NDMA level of [redacted] VCDs and the highest reported NDMA level of [redacted] VCDs to *illustrate* not only the highest dose, but the average [redacted] dose patients could experience. At the specific causation phase of this litigation, each individual Plaintiff will present with their own unique level of contamination profile which will be dependent on which defendant manufacturers made their VCDs. Each Defendant who manufactured VCDs containing NDMA and NDEA taken by a Plaintiff would contribute to the total cumulative dose of NDMA and/or NDEA to which the Plaintiff was exposed, but that exposure analysis is properly part of the specific causation phase of this case.

Once again, the case law cited by Defendants does not support their position given the facts of this case. *Zellers v. NexTech Northeast, LLC*, 895 F. Supp. 2d 734 (2012) is a specific causation case that involved escape of Freon refrigerant gas, which is not a genotoxin, and an expert who

Evidence, p. 553

[46] Ex. A, Panigrahy Expert Report, pp. 88-89.

could not testify as to plaintiff's level of exposure and lacked expertise in toxicity of Freon. *Krik v. Exxon Mobil Corp*., 870 F. 3d 669 (2017) is a specific causation asbestos case in which the expert could not offer any evidence on exposure, so it was not admitted. *Rockman v. Union Carbide Corp*., 266 F. Supp. 3d 839 (2017) involved a specific causation case of "bystander exposure for a few weeks" to asbestos which could not be quantified nor supported by occupational studies. In that situation, the Court held the expert couldn't just state "each and every exposure" was sufficient without supportive data. *Yates v. Ford Motor Co*., 113 F. Supp. 3d 841 (2015) is another specific causation case in which the expert could offer no evidence of exposure levels for this plaintiff, which is inapplicable here. Similarly, *Steele v. Aramark Corp*., 535 F. Appx. 137 (2013) was a specific causation case with a finding there was no proof the toluene vapor exposure was a substantial factor in the injury. *McClain v. Metabolife Intl., Inc*., 401 F. 3d 1233 (2005) as cited, is not applicable to our facts as it involved a non-genotoxin, with an expert who ignored dose response and level of exposure needed for injury. *Rider v. Sandoz Pharms, Corp*., 295 F. 3d 1194 (2002) and *Glastetter v. Novartis Pharms. Corp.*, 252 F. 3d 986 (2001) are specific causation cases for Parlodel in which the Court found the FDA statement withdrawing approval of the drug for lactation was not proof of causation by itself. *Mancuso v. Consolidated Edison Co*., 967 F. Supp. 1437 (1997) was a specific causation case with a plaintiff expert with no toxicity experience or training who argued alleged levels of PCB soil contamination over NYSDEC levels was proof of specific causation which was disallowed by the Court.

The cumulative exposure theory has been accepted in various circuits, including in the First and Second Circuits. [47] Additionally, the Middle District of Pennsylvania recently ruled that the

[47] Coffin v. AMETEK, Inc., 2020 WL 5552113 (1st Circuit); Berman v. Mobil Shipping & Transportation Co., 2019 WL 1510941 (2nd Circuit)

"cumulative theory of exposure" (which was distinguished from the "each and every breath theory) has been found reliable by numerous Pennsylvania and federal courts."[48]

POINT VI: DR. PANIGRAHY ADDRESSES BIOAVAILABILITY OF NDMA and NDEA IN "DOWNSTREAM ORGANS" AND HAS NOT "CONFLATED CANCER GENERALLY WITH THE SPECIFIC CANCERS".

Defendants' argument that Dr. Panigrahy doesn't account for the "first pass metabolism" is completely without merit. This is clearly addressed in his report as he has entire sections devoted to this topic. One is entitled "Animal Studies Support that NDMA is Distributed Throughout the Mammalian Body" and the other is entitled "Bioavailability of NDMA is Dramatically Higher in Larger Species than in Rodents."[49]

First pass metabolism (aka as first pass effect) refers to the phenomenon that a drug gets metabolized at a specific location in the body that results in a reduced concentration reaching the systemic circulation. For NDMA, it is the liver's efforts to eliminate the agent before reaching other organs in the body that is known as the first pass effect which affects NDMA's "bioavailability". Dr. Panigrahy spends pages of his report addressing the peer reviewed studies that show the bioavailability of NDMA is "dramatically higher in larger species than in rodents." He cites evidence that only 8% of NDMA was found in the blood of the rat and hamster while 49% was bioavailable in the monkey; 67% was bioavailable in the pig; and 93% was bioavailable in the dog. Since a large portion of an oral dose of NDMA in these larger animals reach the systemic circulation, Dr. Panigrahy explains that NDMA is available to be metabolized in organs other than the liver.[50] His report cites to the various published scientific studies that support these findings including the Gombar studies.[51] Dr. Panigrahy then, in each individual cancer section of

[48] Gorton v. Air & Liquid Sys. Corp., 2020 WL 4193649, at *2 (M.D. Pa. July 21, 2020)
[49] Ex. A, Panigrahy Expert Report, pp. 76-80.
[50] Ex. A, Panigrahy Expert Report, pp. 76-80.
[51] Ex. J, Gombar, et.al, *Interspecies scaling of the pharmacokinetics of N-nitrosodimethylamine*; Cancer

his report,[52] explains how it is biologically plausible that NDMA or NDEA causes that individual type of cancer. Considering the above, the defense's assertion that Dr. Panigrahy fails to address "first-pass metabolism" is clearly without merit.

POINT VII: DR. PANIGRAHY DOES NOT RELY UPON THE FDA'S DAILY ACCEPTABLE DAILY LIMITS AS A PROXY FOR GENERAL CAUSATION.

Dr. Panigrahy does not use the FDA Acceptable Limits (AI) of 96 ng/day for NDMA and 26.5 ng/day for NDEA for his general causation or dose opinion. He simply acknowledged these levels as the only scientifically accepted AIs for NDMA and NDEA by the regulatory agencies. The FDA AIs for NDMA and NDEA are not used in his cumulative exposure methodology derived from the peer reviewed dietary and occupation studies as discussed in detail above.[53]

Dr. Panigrahy does use these Acceptable Daily Intake limits to illustrate that NDMA and NDEA are known potent genotoxins, and therefore, tightly controlled. The FDA AI limit is derived from the ICH M7(R1) Guidance for Industry which provides a methodology to determine Acceptable Daily Intake for M7 Class 1 impurities (known mutagenic carcinogens) like NDMA and NDEA **with no established threshold mechanism**.[54] The primary literature relied upon by the FDA for NDMA and NDEA is the Peto[55] rat study and was used to establish the FDA's AI of 96 ng/day for NDMA and 26.5 ng/day for NDEA as the maximum allowed by the FDA for a drug taken once per day.

Res 50, 4366-4370 (1990); and Gombar, et. al., *Pharmacokinetics of N-nitrosodimethylamine in swine*. Carcinogenesis 9, 1351-1354 (1988); and Gombar, et.al, *Pharmacokinetics of N-nitrosodimethylamine in beagles*. Cancer Res 47, 343-347 (1987).

[52] Ex. A, Panigrahy Expert Report, pp. 96-201.

[53] Ex. C, Panigrahy deposition at pp. 359-364.

[54] Ex. E, ICH M7 (R1) Guidance for Industry: Assessment and Control of DNA reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (March 2018); Ex. D, Control of Nitrosamine Impurities in Human Drugs, Guidance for Industry, FDA Center for Drug Evaluation and Research (CDER), Feb. 2021, Appendix B.

[55] Ex. K, Peto (1991) *Effects on 4080 Rats of Chronic Ingestion of N-nitrosodiethylamine or N-nitrosodimethylamine: A Detailed Dose Response Study,* Cancer Research, 51: 6415-6451.

Defendants allege that Plaintiffs' epidemiology expert testified that there was likely no increased risk with taking valsartan for 30-90 days. The important point at this stage is that the levels seen here were unacceptable due to the risk, and the higher the levels of NDMA and/or NDEA exposure in the VCDs, the fewer number of days are needed to reach the cumulative dietary or Hidajat exposures that result in a statistically significant increased risk of cancer. It all depends on when a patient's cumulative NDMA and/or NDEA exposure reaches those cumulative levels. There is nothing in Dr. Panigrahy's report about a higher risk of cancer after 30-90 days, so this is a red herring.

POINT VIII: DR. PANIGRAHY DID NOT IGNORE HUMAN DNA REPAIR.

Dr. Panigrahy testified that human DNA repair systems can repair mutations but noted that these genotoxins disrupt and impair the DNA repair process.[56] Dr. Panigrahy discusses this phenomenon in depth as Key Characteristics #3 and #7: Both NDMA and NDEA impair DNA repair and cause genomic instability which is an increased tendency of genome alteration during cell division.[57,58] He also testified that NDMA/NDEA can cause cancer through mechanisms other than DNA mutations including (which are included as key characteristics of carcinogens): impaired DNA repair by these agents leading to genomic instability; chronic inflammation, oxidative stress, immunosuppression and apoptosis.[59] He explained that even with an intact MGMT DNA repair system, cancer can still be induced by NDMA/NDEA by these other mechanisms.[60] Lastly, patients who develop cancer have DNA repair systems that failed to protect them which is why in the dietary studies and Hidajat occupational study there are statistically

[56] Ex. C, Panigrahy deposition, pp. 227-228, 288.
[57] Ex. A, Panigrahy Expert Report, pp. 59-61 and 162.
[58] Ex. C, Panigrahy deposition, pp. 227-228.
[59] Ex. C, Panigrahy deposition, pp. 227-228; 287-288.
[60] Ex. C, Panigrahy deposition, pp. 227-228, 287-288, 42-46; Ex. A, Panigrahy Expert Report, pp. 42-46.

significant increased risks of certain cancers with increased exposure to NDMA (or NDEA in the Zheng study).

POINT IX: THERE IS SCIENTIFIC BASIS FOR AN OPINION THAT NDEA CAUSES CANCER IN HUMANS.

NDEA is a less studied Class 1 genotoxin carcinogen than NDMA. There are many animals but only one human epidemiology study discussed in Panigrahy's report that quantified NDEA exposure and increased risk of pancreatic cancer. Like NDMA, there have been no randomized control studies on humans ingesting NDEA, which would be unethical.

Dr. Panigrahy describes extensive evidence of NDEA cancer bioassays and animal tissue studies for each cancer type involving NDEA exposure in his report. There is less available published research for NDEA but no lack of scientific basis for his opinion that NDEA is a human carcinogen. Dr. Panigrahy cited over **178** NDEA studies out of 586 peer reviewed studies. He systematically identified studies for each cancer type for small and large animals, *in vitro* and cellular studies involving the carcinogenic effect of NDEA. [61] He provides a detailed analysis of the available animal and human evidence of NDEA's genotoxic and carcinogenic properties.[62] He performed a Bradford Hill analysis and reviewed the available evidence in conjunction with the 10 Key Characteristics of carcinogenesis for this genotoxin. Similar to NDMA, NDEA is also used as an agent to cause cancer in laboratory animals and is known for its ability to cause cancer *by a single dose* in over 17 studies.[63] NDEA is carcinogenic in all animal species tested and is deemed to be a likely carcinogen in humans by IARC and NTP among others.[64] **NDEA is a similar nitrosamine to NDMA although considered 3x more potent than NDMA, which is why the**

[61] Ex. A., Panigrahy Expert Report, pp. 148-201
[62] Ex. A, Panigrahy Expert Report, pp. 148-195.
[63] Ex. A, Panigrahy Expert Report, pp. 150-151 (containing cites to the supporting studies).
[64] Ex. A, Panigrahy Expert Report, pp. 150-152.

FDA has a lower AI for NDEA at 26.5 nanograms per day vs 96 nanograms per day for NDMA.[65]

Dr. Panigrahy showed that both NDMA and NDEA are metabolized by cytochrome P-450 enzymes which are expressed in many tissues, organs, and cells throughout the human body and that many of the mechanisms of cancer causation for NDMA apply to NDEA.[66]

There is only one dietary study for NDEA, Zheng, which quantified NDEA exposure and risk of pancreatic cancer. Zheng's study showed statistically significant increased risk of pancreatic cancer for Quartiles 3 and 4.[67]

An expert's opinions on cancer causation can be accepted in the absence of human epidemiology. *In re Paoli Railroad Yard PCB Litigation*, 35 F. 3d 717 (1994) is a Third Circuit case in which the District Court's grant of summary judgment on claims for medical monitoring was reversed on appeal holding:

> *Here, where the EPA has relied on animal studies to conclude that PCBs are a probable human carcinogen, where there is reason to think that animal studies are particularly valuable because animals react similarly to humans with respect to the chemical in question, and where the epidemiological data is inconclusive and some of it supports a finding of causation, we think that the district court abused its discretion in excluding the animal studies. Certainly, the evidence meets the relevance requirements of Rule 402 and we think, after taking a hard look, that it also meets the reliability requirement of Rules 702, 703 and 403. In re Paoli, at 781.*

An expert's opinion is reliable on general causation when not based on epidemiological data if the expert's testimony and methodology is both relevant and reliable as epidemiological studies are not necessarily required to prove causation. *Benedi v. McNeil-P.P.C., Inc.,* 66 F.3d 1378 at 1384. *Globetti v. Sandoz Pharms. Corp*., 111 F. Supp. 2d 1174, 1179. See also, *Schott v.*

---

[65] Ex. A, Panigrahy Expert Report, pp. 148-149 (with cites to supporting studies).
[66] Ex. A, Panigrahy Expert Report, pp. 177-182.
[67] Ex. T, *Dietary N-nitroso compounds and risk of pancreatic cancer; results from a large case-control study.* Zheng, et. al., Carcinogenesis, 2018 1-9.

I-Flow Corp, 696 F. Supp 2d 898 at 905. There is scientifically reliable evidence that NDEA acts similarly in its carcinogenic properties as NDMA, except for NDEA being approximately three times more potent. The limited availability of human studies should not impede the reliability of Dr. Panigrahy's opinions on NDEA when the animal data and *in vitro* tissue studies are so clear.

POINT X: THERE IS OVERWHELMING EVIDENCE FROM MANY RELIABLE SOURCES THAT NDMA AND NDEA ARE HUMAN CARCINOGENS.

NDMA and NDEA are probable human carcinogens and should be treated "for all practical purposes" as causing cancer in humans.[68] The FDA in its General Advice to drug manufacturers of angiotensin II receptor blockers (ARBs) specifically stated that

"**Nitrosamine compounds are potent genotoxic carcinogens in several nonclinical species and are classified as probably human carcinogens by the International Agency for Research on Cancer (IARC)…Due to their known potent carcinogenic effects and because it is feasible to limit these impurities by taking reasonable steps to prevent or eliminate their presence, FDA has determined that there is no acceptable specification for nitrosamines in ARB API and DP. Therefore, FDA advises that nitrosamines should be absent (i.e., not detectable as described below) from ARB API and ARB drug products."**[69]

The World Health Organization's publication addressing the carcinogenicity of NDMA considered the animal studies, mechanistic studies, and human dietary studies, and concluded: **"NDMA is highly likely to be carcinogenic to humans**".[70]

The Defendants' 30(b)(6) witnesses [redacted]. For example, ZHP subsidiaries Prinston and Solco, who marketed and distributed ZHP finished dose in the United States, stated in the recall, [redacted]

[68] Ex. L, *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some N-Nitroso Compounds*, Vol. 17, 1978, p. 107 for NDEA and p. 152 for NDMA.
[69] Ex. M, FDA General Advice to ARB drug manufacturers, p. 1.
[70] Ex. N, Liteplo & Meek, WHO *Concise International Chemical Assessment Document 38- N-Nitrosodimethylamine*, 2002, p. 23, 4.

[redacted]. ,,[71]

ZHP 30(b)(6) witness [redacted] [72] [redacted] [73] Hetero's 30(b)(6) witness [redacted] [74]

Defendants' argument that irrelevant data was used by analyzing results for API is misplaced as [redacted] on both API and Finished Drug product show equivalent contamination levels.[75] Further, [redacted] [76]

CONCLUSION

Dr. Panigrahy's opinions are based on the totality of available scientific data. He used accepted methods to identify a human lifetime cumulative exposure dose based on the human observational studies to establish the cumulative exposures which result in an increased risk of various cancers in humans. Defendants' arguments at most go to their interpretation of the studies which goes to weight and not reliability. Defendants' motion should be denied in all respects.

Respectfully submitted,

Rosemarie Riddell Bogdan

[71] Ex. O, SOLCO00024226.
[72] Ex. P, Min Li 4/22/21 Dep. Tr., 696:3-697:10.
[73] Ex. P, Min Li 4/22/21 Dep. Tr., 647:9-648:5.
[74] Ex. Q, B. V. Ramarao 4/29/21 Dep. Tr. 259:20.
[75] Ex. R, ZHP/SOLCO00028261.
[76] Ex. S, Hai Wang 3/10/21 Dep. Tr. 112:2-118:17; Ex. R, SOLCO00028261.

CERTIFICATE OF SERVICE

I hereby certify that on December 1, 2021, I electronically filed the foregoing document with the Clerk of the Court using the CM/ECF system which will send notifications of such filing to the CM/ECF participants registered to receive service in this MDL.

/s/ Rosemarie Riddell Bogdan

Rosemarie Riddell Bogdan